Influence of Type of Surgery on the Occurrence of Parasympathetic Reinnervation After Cardiac Transplantation

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Background—Cardiac autonomic reinnervation after human cardiac transplantation has been demonstrated frequently but to date only for sympathetic efferents. Standard surgical techniques leave many parasympathetic branches intact in the original atria and thus with less stimulus to reinnervate the donor atria.

Methods and Results—We used changes in the RR-interval power spectrum induced by sinusoidal modulation of arterial baroreceptors by neck suction at different frequencies to detect both parasympathetic and sympathetic reinnervation in 79 subjects with “standard” and 10 “bicaval” heart transplants. In 24 subjects (17 standard and 7 bicaval), the protocol was repeated 6 and 11 months after transplantation. Neck suction at 0.20 Hz produced a component at 0.20 Hz in the RR-interval spectrum not due to respiration (fixed at 0.25 Hz), which suggested parasympathetic reinnervation, in 4 of 10 bicaval but in only 2 of 79 standard transplant subjects (whose recipient atria underwent >50% resection to remove scars of previous interventions), P<.001. In only 1 (bicaval) transplant subject was parasympathetic reinnervation present 6 months after transplantation (confirmed 3 months later); in 4 subjects, it was absent at 6 months but appeared after 11 months after transplantation. Atropine (0.04 mg/kg IV) abolished the response to fast (0.20 Hz) and reduced that to slow stimulation, confirming the presence of parasympathetic reinnervation (4 subjects).

Conclusions—Parasympathetic reinnervation depends on the surgical technique: because bicaval surgery cuts all sympathetic and parasympathetic nerves, regeneration might be stimulated similarly in both branches. Standard surgery cuts only ≈50% of sympathetic fibers; most recipient parasympathetic axons remain intact, hence their regeneration might not be stimulated. (Circulation. 1998;97:1368-1374.)

Key Words: heart rate n transplantation n arrhythmia n baroreceptors

I n a previous study,1 we described and validated a test of the occurrence of autonomic reinnervation after cardiac transplantation based on sinusoidal modulation of the arterial (carotid) baroreceptors by external neck suction. Although the use of two separate frequencies of modulation (0.1 Hz and near-respiratory frequency) allowed us to establish the separate occurrences of parasympathetic and sympathetic reinnervation, we found signs attributable to sympathetic reinnervation in 50% of the subjects but no parasympathetic reinnervation in any of them. This lack of parasympathetic reinnervation in humans was also found in other studies by us2 and by others.3-7

In the present report, we suggest that the surgical technique could be responsible for these results. Because the “standard” technique leaves most of the recipient atria intact,8 most of the parasympathetic axons also remain intact and thus might not be stimulated to regenerate. Conversely, the so-called “bicaval” technique (by which the whole recipient heart, including the entire atrial junctions of both superior and inferior venae cavae are removed and substituted with equivalent components of the donor heart) cuts 100% of both parasympathetic and sympathetic fibers and can therefore stimulate both branches to regenerate. This technique was already described in early dog experiments that provided evidence of parasympathetic reinnervation10 but has been introduced only recently into clinical practice; its effects in terms of cardiac reinnervation are unknown in humans. We therefore compared the two techniques in terms of their ability to produce reinnervation in the parasympathetic and in the sympathetic branches in humans.

Methods

Subjects
We studied 89 orthotopic heart transplant recipients, 10 with bicaval and 79 with standard surgery. After the introduction of the bicaval
subject is due to reflex parasympathetic activity.1 We also showed that the 0.20-Hz peak in the RR-interval spectrum of the normal subject (Fig 1): the 0.20-Hz peak is due to the pure effect of the mechanical and baroreflex components. We previously showed that the 0.25-Hz peak is due to the effect of breathing (which influences the heart period by impedance pneumography), noninvasive blood pressure (by Finapres, Ohmeda), and the pressure within the neck collar on a bicaval surgery patient.1

Recording Protocol, Data Acquisition, and Analysis

The protocol and methodology were identical to those previously reported.1 During each observation we recorded ECG, respiration (by impedance pneumography), noninvasive blood pressure (by Finapres, Ohmeda), and the pressure within the neck collar on a Macintosh II computer at 500 Hz per channel. All recordings were made during controlled breathing at 0.25 Hz (15 breaths per minute) to obtain stable and narrow-band respiratory fluctuations. We obtained recordings during (1) 4-minute baseline, (2) 2-minute sinusoidal suction at 0.1 Hz (slow stimulation, 0 to −30 mm Hg), and (3) 2-minute sinusoidal suction at 0.2 Hz (fast stimulation, 0 to −30 mm Hg), ie, close to but distinct from the controlled respiratory frequency of 0.25 Hz.

Time series of the RR interval, respiration, neck pressure, and blood pressure were obtained and analyzed by autoregressive power spectral analysis. The coherence function was used to test whether the respiratory and the time since transplantation. Differences between proportions were assessed by the Student's t test. Differences within groups, and a nonpaired t test was used for differences between groups. Simple linear regression analysis was used to assess the relationship between the observed changes induced by neck suction and the time since transplantation. Differences between proportions were assessed by the chi-square test.

Results

Bicaval Versus Standard Surgical Techniques

Baseline Data

Fig 2 summarizes the results obtained in all 89 subjects examined, subdivided into two groups according to the type of surgery adopted for heart transplantation. For those 24 subjects who were examined twice (5-month follow-up), this figure includes only the results of the second (ie, final) observation. Complete results of the follow-up are reported in the next section below and in Fig 3.

All subjects who received transplants showed low resting RR interval and low RR-interval variability. Low-amplitude, HF components in RR-interval variability coherent with the

Figure 1. RR-interval time series and autoregressive power spectra obtained from a normal subject, from a heart transplant (TX) recipient with standard surgery, and from a TX recipient with bicaval surgery, the latter before and during atropine. Note two peaks in normal subject due to respiration (0.25 Hz) and neck suction (0.20 Hz). Note presence of only 0.25-Hz component in standard transplant and of both components in bicaval transplant, with disappearance of 0.20-Hz component after atropine, confirming parasympathetic reinnervation. To allow comparisons, spectra obtained from TX recipients are shown both at high magnification and at same scale as for normal subject.

that during slow stimulation, the presence of a reflex 0.1-Hz peak in the RR interval indicated sympathetic reinnervation.1

Atropine Testing

After the recordings obtained during the first examinations were analyzed, the 4 bicaval patients who showed a clear response to the fast neck suction stimulation were restudied (3 to 6 months after the first examination) after injection of 0.04 mg/kg atropine IV according to the same protocol.

**Clinical Characteristics of the Heart Transplant Recipients**

<table>
<thead>
<tr>
<th></th>
<th>Bicaval Surgery</th>
<th>Standard Surgery</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Recipient age, y</td>
<td>54±2</td>
<td>50±1</td>
<td>NS</td>
</tr>
<tr>
<td>Donor age, y</td>
<td>34±6</td>
<td>36±2</td>
<td>NS</td>
</tr>
<tr>
<td>Months since transplantation</td>
<td>9.0±0.6 (7-12)</td>
<td>32±6 (2-106)</td>
<td>0.025</td>
</tr>
<tr>
<td>Current therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine, mg</td>
<td>328±37</td>
<td>260±20</td>
<td>NS</td>
</tr>
<tr>
<td>Azathioprin, mg</td>
<td>70±5</td>
<td>64±4</td>
<td>NS</td>
</tr>
<tr>
<td>Tacrolimus, mg</td>
<td>0 (n=0)</td>
<td>1.2±0.4 (n=9)</td>
<td></td>
</tr>
<tr>
<td>Oral steroids, mg</td>
<td>16.4±6.0</td>
<td>8.2±0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>ACE inhibitors, n</td>
<td>1/10</td>
<td>34/79</td>
<td>0.05</td>
</tr>
<tr>
<td>Calcium antagonists, n</td>
<td>3/10</td>
<td>27/79</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics, n</td>
<td>5/10</td>
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respiratory signal, which we previously showed to depend on nonautonomic mechanisms, were also present in all subjects. Low-amplitude, LF components in RR-interval variability not due to spurious slow respiration could be identified in a large number of subjects: 36 of 79 in the standard surgery group and 6 of 10 in the bicaval group. The power of these LF oscillations was positively correlated with months since transplantation ($r = 0.221$, $P = 0.041$, Fig 4). As in previous studies, the scattergram of the LF power versus months since transplantation showed a triangular distribution, with the LF values clustering toward 0 earlier after transplantation and spreading out progressively with increasing time since transplantation. Conversely, the power in the HF fluctuations did not show any trend with months since transplantation ($r = 0.026$, $P = \text{NS}$, Fig 4).

Effect of HF Neck Suction
During HF neck suction, we found the appearance of a second small but distinct peak in the RR-interval power spectrum in the HF band (Fig 1) in 4 of 10 recipients of bicaval heart transplantation. As a consequence, the power at 0.20 Hz increased from 0.00±0.00 to 0.33±0.18 ln(ms$^2$) in the whole bicaval group. The power in the 0.20-Hz peak was smaller than that associated with the respiratory peak (2.84±0.44, $P<0.001$) and was in the range of ~0.3% to 1% (in terms of power) of that seen in normal subjects. The appearance of this component after heart transplantation is indicative of a reflex transmission of the neck stimulus from the carotid baroreceptors to the heart. The absence of coherence between respiration and RR-interval spectra in the 0.20-Hz region confirmed that this was not due to spurious breaths at 0.20 Hz. According to our previous work, this indicates parasympathetic reinnervation. Because of the autoregressive spectral technique and the strictly controlled respiration, very little or no noise was present in the 0.20-Hz region, and therefore the presence of this component could be easily identified if present.

Conversely, HF neck suction was able to generate similar fluctuations in only 2 of 79 recipients of standard heart transplantation. Of these 2 subjects, 1 had undergone transplantation 44 months earlier and was never studied previously; the other had undergone transplantation 12 months earlier. Signs of parasympathetic reinnervation were absent in this subject during a previous study at 6 months after transplantation (see follow-up). Interestingly, both these subjects had undergone heart transplantation after a previous intervention for myocardial revascularization. In both these subjects, the surgeon performed the standard technique but removed a larger than usual (>50%) part of the right atrial wall to eliminate those portions with scars due to previous cannulations. In 41 of 79 recipients of standard heart transplantation, full documentation was available and indicated that a similar intervention for myocardial revascularization was performed before transplantation in 13 subjects. Thus, previous surgery appeared to be significantly associated with an increased probability of parasympathetic reinnervation (2 of 13 versus 0 of 28, $P<0.05$, $\chi^2$ test). The proportion of patients showing evidence of parasympathetic reinnervation was significantly higher for the bicaval than for the standard surgery ($P<0.001$, $\chi^2$ test).
Effect of LF Neck Suction
In both groups, LF neck suction at 0.1 Hz significantly increased the power in the LF band (Fig 2).

The power in the LF band increased in the 42 subjects (36 in the standard and 6 in the bicaval surgery group) in whom LF oscillations were present at baseline and generated LF oscillations in 7 more subjects (all from the standard surgery group) in whom spontaneous LF oscillations were not evident at baseline. The proportions of subjects who responded to LF neck suction were similar in the two groups (43 of 79, 53%, in the standard and 6 of 10, 60%, in the bicaval surgery group, \( P < 0.05 \)). The power of the LF during neck suction at 0.1 Hz correlated with months since transplantation \((r = 0.228, P = 0.033 \) Fig 4). Like the relationship with resting LF, the scattergram showed a diverging distribution, with the LF values clustering toward 0 earlier after transplantation and spreading out progressively with increasing time since transplantation.

Follow-up
Mean results of a 5-month follow-up are shown in Fig 3 for the two subsets of subjects. At the first observation, early after transplantation, only 1 subject from the bicaval surgery group and none from the standard surgery group showed any reflex response to the 0.20-Hz neck suction, indicative of little or no early parasympathetic reinnervation. Conversely, 3 of 7 subjects from the bicaval surgery group and 4 of 17 from the standard surgery group showed a clear response to the 0.10-Hz neck suction, indicative of early sympathetic reinnervation. After an average period of 5 months (3 to 6 months), 4 of 7 subjects from the bicaval surgery group and 1 of 17 from the standard surgery group showed a clear response to the 0.20-Hz neck suction, indicative of greater parasympathetic reinnervation in these subjects. The standard surgery subject (see above) was not a pure case of standard surgery (as described in the previous section on the effect of HF neck suction) but rather had an unusually high proportion of the recipient right atrium removed.

In addition, 5 of 7 subjects from the bicaval surgery group and 12 of 17 from the standard surgery group showed a clear response to the 0.10-Hz neck suction, indicative of sympathetic reinnervation.

Effect of Atropine
During the second test in the 4 subjects from the bicaval surgery group who showed signs of parasympathetic reinnervation, we repeated the protocol after injection of 0.04 mg/kg atropine IV. After atropine, the heart rate increased from 78 ± 1 to 84 ± 2 bpm \((P < 0.05)\), the respiratory \((0.25-\text{Hz})\) component did not drop significantly \([\text{from 1.36 ± 0.50 to 1.26 ± 0.47 ln(ms}^2])\), but during 0.20-Hz neck suction stimulation, the 0.20-Hz component disappeared almost completely \([\text{from 1.28 ± 0.27 to 0.25 ± 0.16 ln(ms}^2]), \(P < 0.025)\], while the response to 0.1-Hz stimulation was reduced but not abolished \([\text{the LF power rose from 1.15 ± 0.32 to 2.89 ± 0.29 ln(ms}^2]), \(P < 0.001\) before atropine and from 0.69 ± 0.27 to 1.13 ± 0.38 ln(ms}^2), \(P < 0.05\) after atropine\] (Figs 1 and 5). Coherence analysis showed that the 0.10-Hz and 0.20-Hz components observed during neck suction were not due to irregular respiration. The respiratory signal showed a relative reduction in tidal volume of 13 ± 6% after atropine compared with baseline, which could have explained the reduction observed in the 0.25-Hz component.

Discussion
Main Findings of the Present Study
In our previous study,\(^1\) we showed how to detect both sympathetic and parasympathetic reinnervation, but until recently we and others\(^7\) found the presence of only sympathetic reinnervation after cardiac transplantation. The reasons for the lack of parasympathetic reinnervation remained unexplained.
In the present study, we have now found that a rudimentary parasympathetic reinnervation can be demonstrated after cardiac transplantation. This seems to occur rather commonly in subjects who underwent the new bicaval surgical technique (4 of 10), whereas it is a rare event (2 of 79) after the standard technique: the proportion of parasympathetic reinnervation was significantly higher \( (P < .001) \) in the bicaval than in the standard surgery group. Furthermore, it seems that the standard technique might be modified to provoke parasympathetic reinnervation, because in both subjects of the standard surgery group with signs of parasympathetic reinnervation, the recipient atria underwent a substantial reduction (>50%) to eliminate scars due to previous interventions of revascularization. The present study confirms that a rudimentary sympathetic reinnervation is relatively frequent, occurring in \( \approx 50\% \) of the heart transplant recipients. Thus, whereas after standard surgery only sympathetic reinnervation is common, after bicaval surgery the frequencies of parasympathetic and sympathetic reinnervation are similar (4 of 10 versus 6 of 10, respectively, 9 months after transplantation).

All this indicates that the surgical technique plays a major role in the probability of subsequent development of parasympathetic reinnervation. Because of the shorter time from transplantation to our study, the bicaval group was treated with higher doses of steroids at the time of the study (Table). However, at equivalent times of follow-up, the two groups received the same amount of steroids regardless of the surgical technique adopted. Therefore, although a possible role of steroids in enhancing cardiac nerve regeneration could not be excluded,13 treatment with steroids probably does not explain the differences observed between the two surgical techniques.

Previous Reports of Parasympathetic Reinnervation

The few reports that suggested the occurrence of parasympathetic reinnervation were invariably confined either to single cases14 or to very limited observations.15 In addition, in all these reports there was no clear demonstration that the vagus was unequivocally responsible for the observed changes in heart rate variability. The parasympathetic effect was deduced from the observation of “respiratory” variations in heart rate similar to those exerted by the vagus. Although parasympathetic reinnervation cannot be excluded in these reports, it might be questioned, because it has been shown that respiration can determine changes in heart period by a direct mechanical effect on the denervated heart, without the need for autonomic modulation.1,2,11,12 In these subjects, the use of atropine to detect a reduction in respiratory sinus arrhythmia is also meaningless if one does not ascertain that there were no changes in the respiratory amplitude (ie, tidal volume). The occurrence of a vasovagal-like reaction was often reported after cardiac transplantation,14–17 but in most studies, this was found in patients with absent reinnervation.13–17 All these considerations clearly indicate that parasympathetic reinnervation is either absent or at least unusual after heart transplantation performed with the standard technique.

Rationale and Methodology for Evaluating Parasympathetic Reinnervation After Heart Transplantation

The variation in the heart period, respiratory and nonrespiratory (ie, due to the 0.1-Hz rhythm), is to a large extent (~95%; References 11, 18, and 19) due to the modulation of the autonomic nervous system in the normal subject, but after heart transplantation the largest component of variability is due to the respiratory modulation exerted by direct mechanical stretching of the donor atria. This component does not disappear after parasympathetic blockade1 and maintains a relationship with the rate of change in respiration (respiratory flow1,11,12,19). Hence, because of the presence of this mechanical component due to the inspiratory increase in venous return, any attempt to quantify the parasympathetic activity in the transplanted heart cannot use only a respiratory modulation of heart period.

To reliably detect the presence of a parasympathetic modulation, we then “split” the autonomic from the mechanical effect of respiration on the RR interval by using neck suction at a frequency in the HF range (0.20 Hz) similar to but distinct from that of respiration (maintained at 0.25 Hz by controlled breathing). We and others have found that in this frequency range, only the parasympathetic (and not the sympathetic) activity can modulate the heart period11,19; in addition, neck suction is a “pure” autonomic stimulus that is not associated with any hemodynamic effect other than reflex.1 We have also shown that the parasympathetic is the only determinant of the neck suction–induced component at 0.20 Hz, because this component is abolished completely by atropine,1 even in conditions of sympathetic activation (standing posture20). Other factors, such as catecholamines, are unlikely determinants, because this modulation appears to be too fast for circulating substances. The absent response of the recently transplanted heart to any kind of autonomic stimulation early after transplantation indicates that the term “denervated” could be maintained for the donor heart, even though the donor heart maintains a rich autonomic innervation (and therefore is “disconnected” only from the recipient atria).

Influence of Surgery on the Possibility of Parasympathetic Reinnervation After Heart Transplantation

The hypothesis of possible reinnervation after heart transplantation is based on the idea that because the donor heart is denervated after transplantation, the nerves sooner or later should regenerate. However, a nerve has some probability of regeneration only if it has been cut.21 Also, because nerve regeneration normally occurs from the proximal termination downward, regeneration should depend on the number of fibers (parasympathetic or sympathetic) that have been cut in the proximal (and not the distal) structure. Therefore, the crucial thing for reinnervation is the recipient and not the donor heart.

The standard surgical technique involves cutting of the recipient heart at the level of the atrioventricular connection.8 In the normal heart, most (although not all) parasympathetic fibers that enter the heart stop in the atria, whereas nearly half
of the sympathetic fibers progress to the ventricles. Hence, with the standard surgery (Fig 6, left), if the donor heart is by definition denervated, the majority of the parasympathetic endings of the recipient heart actually remain intact, whereas about half of the sympathetic fibers (all the fibers directed to the ventricles) are severed well before their termination. This is confirmed by the common finding that the changes in heart rate of the recipient atrium remain under parasympathetic control.16,23 This explains why only sympathetic fibers tend to show evidence of regeneration after the standard technique, whereas the parasympathetic fibers, by remaining to a large extent intact, have (for the majority) no apparent reason to regenerate. This also explains why the donor atrium might remain parasympathetically denervated but could receive some sympathetic terminations.

As a consequence, the probability of parasympathetic reinnervation should increase if the parasympathetic fibers in the remnant of the recipient heart are also cut to a larger extent, as happens for the sympathetic fibers. This was in fact observed in 2 subjects who previously received transplants with the standard technique, who both underwent a >50% reduction in recipient right atrium and consequent interruption of a more relevant number of parasympathetic fibers.

Recently, a different surgical technique (called bicaval or whole-heart technique) has been introduced into practical use, by which the whole recipient heart, including the entire atrial junctions of both superior and inferior vena cavae, was removed and substituted with equivalent components of the donor heart (Fig 6, right). In this case, parasympathetic and sympathetic fibers directed to the heart are both 100% severed well before their termination. This should constitute a stimulus for regeneration identical for both sympathetic and parasympathetic fibers. This technique has been introduced only recently, so only subjects a few months after transplantation are available thus far, but our results clearly indicate that the probability of observing parasympathetic reinnervation is similar to that of sympathetic reinnervation. In contrast, the probability of observing parasympathetic reinnervation with the standard technique is very low or zero regardless of time since transplantation, unless more extensive removal of the recipient atria is performed.

Like sympathetic reinnervation, parasympathetic reinnervation progresses over time. Very few subjects showed signs of early reinnervation after 6 months from transplantation, but the proportion increased equally after a 5-month follow-up, that is, at a time (in the range of 1 year) at which we and others previously found evidence of reinnervation in a large proportion of subjects.1–7 The similar follow-ups in the 17 subjects who underwent the standard technique showed similar reinnervation only for the sympathetic branch, and in only one case was parasympathetic reinnervation observed. However, as previously specified, this was not a case of “pure” standard technique.

Cardiac Reinnervation in Experimental Animal Models of Heart Transplantation

Partial reinnervation of both parasympathetic and sympathetic branches was commonly reported after cardiac transplantation in dogs.10,24,25 This different behavior compared with humans remained unexplained or was attributed to a difference in species. In view of the present findings, it is interesting now to note that only when the surgical technique was identical10 or equivalent24 to the bicaval type was parasympathetic reinnervation a common finding. Note that the bicaval technique was frequently used in these early studies in dogs, although it did not come into practical use for humans until very recently. This unappreciated difference between techniques certainly confused our understanding of the mechanisms of reinnervation. Our present findings therefore suggest that the different results obtained previously in humans and dogs were more likely due to the different surgical techniques and not to species differences.

Conclusions

In the present study, we show that parasympathetic reinnervation could be demonstrated in humans undergoing a new technique of surgery for cardiac transplantation, involving a more extensive atrial resection (total in the case of bicaval technique, only partial in a few cases of the standard technique). This phenomenon is responsible for the similarity of parasympathetic and sympathetic reinnervation, indicating that the type of surgery has a major influence on neural regeneration. This can also explain why in the past only sympathetic reinnervation was commonly observed after the standard surgical procedure of heart transplantation, and parasympathetic reinnervation was not (or only occasionally) found.

Why might reinnervation, and particularly parasympathetic reinnervation, be desirable? The efficacy of the baroreflex-mediated control of blood pressure rests on rapid responses in heart rate, largely mediated by the vagus. Conversely, when sympathetic activity is the only activity present or is largely predominant (for example, during physical exercise), heart rate variability is markedly reduced and cannot buffer the increase in blood pressure. Therefore, reinnervation limited to the sympathetic arm produces only a limited amount of heart rate variability, with less effect in terms of baroreflex-mediated blood pressure control. The adverse effect of the loss of parasympathetic modulation of the cardiovascular system has been known for a long time,26,27 and there is clear
evidence of a protective role of parasympathetic modulation in cardiovascular disease\textsuperscript{28–31}, current medical opinion now believes that increasing parasympathetic activity should be a target for intervention in heart disease.\textsuperscript{28}

The present data suggest a new possibility to increase parasympathetic reinnervation in subjects undergoing heart transplantation, namely, by extensive or total resection of the recipient atria. Thus, the results of the present study could have great clinical relevance, because an increase in control of blood pressure by larger reflex changes in heart rate would lead to a better adaptation to various stimuli and to physical exercise.

Further observations on a longer time scale will provide evidence of whether parasympathetic reinnervation after bicuspid surgery can progress to more than the rudimentary extent observed thus far in our recent transplant recipients and will help to assess methods to potentiate and accelerate its progression.

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References
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